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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,500	11/21/2003	Joseph Chappell	8064-005-CIP-2	8924

32301 7590 06/01/2009

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EXAMINER	
KALLIS, RUSSELL	
ART UNIT	PAPER NUMBER
1638	
MAIL DATE	DELIVERY MODE
06/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,500	CHAPPELL ET AL.	
	Examiner	Art Unit	
	RUSSELL KALLIS	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/02/2009 has been entered.

Claims 10-21 are pending and examined

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 10-21 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION. This rejection is maintained for the reasons of record set forth in the Official action mailed 3/06/2008 and 9/30/2008. Applicant's arguments filed 3/02/2009 have been considered but are not deemed persuasive.

Applicant asserts that reciting "produced in the absence" in the claims is a mere restating of the original language (response page 7). Applicant has not made a convincing argument for "produced in the absence" being the equivalent of "not produced in the absence"; and thus contrary to Applicants' arguments, Applicants have not conformed to the accepted standard with

respect to using equivalent terms. This is easily ascertained by examining the logic of the statement in light of the evidence in the specification. The results in the specification shows that there is no ratio of products produced when there is a single domain present (see figures 4 and 5), so there is not more than one product produced in the absence of one of the two domains; and thus there is no ratio of products.

Claims 10-21 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official action mailed 3/06/2008 and 9/30/2008. Applicant's arguments filed 3/02/2009 have been considered but are not deemed persuasive.

Applicant asserts that an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, they were in possession of the invention and that the claims now have specific language that recites domains involved in the chimeric proteins and relevant identifying characteristics such that there is sufficient structural and functional detail (response pages 11-15).

Applicants' claims recite in claim 10 structural features of two different isoprenoid synthase polypeptide domains (i.e. domains from any monoterpene, diterpene or sesquiterpene synthase or cyclase), and in claim 20 a DDXXD motif; and in claim 10 the generic functional activity of a sesquiterpene synthase. However, the examples provided by Applicant in the specification do not clearly describe the broadly claimed generic invention of the instant claims

because there are insufficient relevant identifying characteristics correlated with sesquiterpene synthase activity which covers a multitude of unspecified isoprenoid synthase polypeptide domains and their respective reaction products. For example, this is made evident in Back K. *et al.* Journal of Biological Chemistry; 31 March 1995, Vol. 270, no. 13, pp. 7375-7381. On page 7380 in Figure 8, the conserved structural features which Applicants argue define their claimed genus, are shown to also encompass a monoterpene cyclase from mint (i.e. a limonene monoterpene synthase having a DDXXD motif) yet would exclude an Aristolochene sesquiterpene synthase from fungi that does not have the same DDXXD motif, but rather has a DDXXE sequence in a radically different location than the other sesquiterpene synthases and the monoterpene synthase from mint; and thus Applicants' invention is not described by the features recited in the claims because those features appear to be held in common with enzymes comprising domains that have different structural parameters, different substrate requirements and produce different generic products i.e. monoterpenes, and diterpenes. Therefore, contrary to Applicants assertions on page 14 of Applicants' response in the last paragraph, Applicant has not reduced to practice the invention as broadly claimed, and thus has not met any of the three criteria as stated by Applicants. In short, Applicants broadly claim DNA encoding a chimeric polypeptide that comprises two different unspecified domains taken from either a monoterpene, diterpene, or sesquiterpene synthase that would produce some unspecified sesquiterpene. However, the specification only describes domains taken from sesquiterpene synthases and the relative placement astride a ration determining domain DDXXD resulting in the products of the two respective sesquiterpene synthases produced from the one chimeric sesquiterpene synthase.

Applicant asserts on page 18-19 that U.S. Patent 5,824,774 shows novel enzymes capable of synthesizing new reaction products is incorrect. There is no mention of new reaction products in the claims or any reduction to practice of new reaction products taught in the specification. Applicant is therefore unable to name specifically those reaction products that are novel.

Applicants' arguments on pages 19-23 suggest that novel isoprenoid products could be produced from the chimeric isoprenoid synthases. However, there is no reduction to practice of this novelty in the instant application or the '774 patent because there is no description of any chimeric isoprenoid synthase that gave rise to a previously unknown isoprenoid.

Applicant asserts that the work of Schalk and Croteau PNAS 2000; pp. 11948-11953; demonstrates post filing evidence for chimeric enzymes generated by a domain swapping process (page 23-24 response). This is not made evident by Schalk *et al.* (PNAS, 97; (22): pp. 11948-11953), where the author's remarks are directed towards the involvement of specific residues and the importance of progressively placed directed mutations into a conserved region and not asymmetrically positioned domains as being determinant for changes in product formation. Further, the swapping of portions of the two respective enzymes analyzed by Schalk *et al.* did not follow recognized intron exon boundaries but rather were determined as a matter of conveniently located restriction sites within the cDNA. Further, the publication date of the cited reference (2000) is well after the date of the priority claim (4/12/1996) of the instant application and does not support Applicant's assertion that the reference provides a description of the broadly claimed genus of chimeric isoprenoid synthase polypeptides and polynucleotides encoding said polypeptides. Moreover, the work of Schalk and Croteau did not result in the formation of a ratio of products characteristic of the two hydroxylases; and thus does not provide

post filing support for written description of a genus. In addition, Applicants' claims are not limited by a ratio determining domain (with the exception of Claim 20), yet the specification teaches that a ratio determining domain is required for the activity of the chimeric polypeptide as claimed.

A summation of Applicants arguments from pages 20-23 of the response is that the product specificity domains comprised within exons 4 and 6 of wild type tobacco and henbane sesquiterpene synthase enzymes respectively together with the ratio domain DDXXD define Applicants' genus of chimeric sesquiterpene synthases, and that one of ordinary skill would be able to identify other chimeric sesquiterpene synthases. It would be remiss upon the Examiner to not point out again that the components that comprise the chimera of claim 10 include domains from monoterpene and diterpene synthases, the domains of which do not react with the substrate of the sesquiterpene synthases and as a result do not share common intermediates with the sesquiterpene synthases and thus the recitation of isoprenoid domains in claim 10 provides insufficient written description for a genus of chimeric polypeptides comprising a domain from a non-sesquiterpene synthases that would synthesize sesquiterpenes.

Claims 10-21 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule encoding a for DNA encoding a chimeric isoprenoid sesquiterpene synthase polypeptide, wherein said chimeric isoprenoid synthase polypeptide comprises a first sesquiterpene synthase domain joined to a second different sesquiterpene synthase domain, astride a ratio determining domain of DDXXD, such that the chimeric isoprenoid sesquiterpene synthase polypeptide encoded by the DNA catalyzes the production of at least one isoprenoid reaction product that is not produced in the absence of

the second isoprenoid synthase polypeptide; and vectors thereof, and plant cells and plants transformed therewith, does not reasonably provide enablement for DNA encoding a chimeric isoprenoid sesquiterpene synthase polypeptide, wherein said chimeric isoprenoid synthase polypeptide comprises a first isoprenoid synthase domain joined to a second different isoprenoid synthase domsin such that the chimeric isoprenoid sesquiterpene synthase polypeptide encoded by the DNA catalyzes: (I) the production of at least one isoprenoid reaction product that is not produced in the absence of the second isoprenoid synthase polypeptide; or (2) the production of more than one isoprenoid reaction product in a ratio differing from the ratio of the products produced in the absence of the second isoprenoid synthase polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record set forth in the Official action mailed 3/06/2008 and 9/30/2008. Applicant's arguments filed 3/02/2009 have been considered but are not deemed persuasive.

It is important to note the change in the enablement scope from the previous rejection.

Applicants' arguments with respect to enablement are largely directed to the argument that experimentation would be required and that what is largely known can be omitted from the specification and if predictability can be minimized by the knowledge in the art (response pages 23-27); see See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. Moreover, the structure of the broad genus of isoprenoid

sesquiterpene synthases that comprise isoprenoid synthase domains from monoterpene and diterpene synthases are largely known to have different substrates and reaction intermediates and would require undue trial and error experimentation for their integration into a chimera polypeptide that would produce two sesquiterpenes if at all.

In addition, since the publication dates of the cited reference Schalk and Croteau PNAS, are well after the date of the claimed priority (4/12/1996) of the instant application the references show that the state of the art did not and still does not support Applicant's broad claim to chimeric isoprenoid sesquiterpene synthases as broadly claimed in claim 10; and contradict Applicant's assertions that the prior art and the relative skill of those in the art provide enablement for making and using the broadly claimed genus of chimeric isoprenoid sesquiterpene synthase polypeptides or provide evidence that the degree of unpredictability is overcome by one of ordinary skill because the work of Schalk and Croteau did not result in the formation of a ratio of products of the two hydroxylases.

Applicant asserts that the Office has not met the burden of countering the actual examples in the specification. Those specific examples are not rejected. Rather the lack of examples is what forms the basis of the rejection and that there is no teaching in the art or Applicants' specification to support the broadly claimed genus.

Applicants' assertions on pages 38-46 have either been addressed in a previous office action or addressed supra. Notably, the lack of a ratio determining domain in the claims is not supported by the specification or the prior art. Further, contrary to Applicants' assertions on page 47 of the response that the starting materials can readily be determined, although the structural features of isoprenoid synthases are similar, where monoterpene and diterpene synthases have a

conserved ratio determining domain and a similar exon structure to the sesquiterpene synthases, the substrate, intermediates and final products participating in the biochemical conversion are not similar enough to allow for broad generalizations for the making of the chimeric sesquiterpene synthases, and thus the starting materials for making the invention have not been delineated to the extent required for an enabling disclosure and the recited case law (See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997)) is appropriate.

Given the unpredictability in the art as to which domains from which plants would tolerate chimerization and produce at least a bifunctional sesquiterpene synthase; the breadth of the claims encompassing any chimeric sesquiterpene synthase comprising any number of enzymatic domains selected from a broad category of unspecified isoprenoid synthases; the lack of guidance in the specification or in the prior art as to which domains of the isoprenoid synthase enzyme family would best serve in the invention; one would not know based upon Applicant's disclosure which embodiments would be inoperable and predictably eliminated. Thus, undue trail and error experimentation would be needed to make and clone a multitude of non-exemplified isoprenoid synthase domains in combination to create a functional sesquiterpene synthase chimera and to test them in a myriad of non-exemplified expression systems for a multitude of non-exemplified isoprenoid sesquiterpene products. Therefore, the invention is not enabled for the full scope of the claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Russell Kallis/
Primary Examiner, Art Unit 1638
May 26, 2009